REMARKS

Status of the Claims

Claims 1, 9, and 29 have been amended without prejudice to or disclaimer of the subject matter therein as described elsewhere herein. Support for the amendments can be found in the specification (see below). Therefore, no new matter has been added by way of claim amendment.

Claims 1-14 and 21-36 are now pending. The Examiner's comments are addressed below in the order set forth in the Office Action.

The Rejections of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 1-10 and 13-14 are rejected under 35 U.S.C. §112, second paragraph. This rejection is respectfully traversed.

The legal standard of definiteness is whether a claim reasonably apprises those of skill in the art of its scope. *See In re Warmerdam*, 33 F.3d 1354, 31 USPQ2d 1754 (Fed. Cir. 1994). Furthermore, the claim must be read in light of the specification. *See, e.g., Credle v. Bond*, 25 F.3d 1566, 30 USPQ2d 1911 (Fed. Cir. 1994).

Because claims 1-10 and 13-14 recite "at least one pharmaceutically active agent," the Examiner reasons that "the claim does not specify how many active agents are included and which active agents are in the pharmaceutical composition." (Office Action mailed April 17, 2002, at page 5, item 5). However, there is no rule that open-ended ranges are indefinite. MPEP § 2173.05(c)II. Furthermore, the specification provides:

> By "pharmaceutically active agent" is meant any pharmaceutically effective compound that is compatible with succinate buffer. Pharmaceutically active agents include, but are not limited to organic drugs, inorganic drugs, antibiotics, proteins, peptides, carbohydrates, lipids, fatty acids, nucleic acids and derivatives thereof. Agents of particular interest include, but are not limited to, IGF-I, Interleukin-2, Interferon-β, Fibroblast Growth Factors I and II, Epotein-α, growth hormone, CNTF, BNDF, TPA, and colony-stimulating factors, ampicillin, pennicillin, chloroquine hydrocholoride, amphotericin B, cephalothin, cefamandole, ceforandied, cefotaxime, cefepime, gentamycin, netilmicin, griseofulvin, clotrimazole, miconozole, betamethasone, cortisol, prednisolone, sumatripan, chlorpheniramine maleate, brompheniramine maleate, enalaprilat, amrinone, dobutamine, thiethylperazine, and the like.

Specification, page 8, lines 3-14. Applicants maintain that, when read in light of the specification, one of skill in the art would be reasonably apprised of the scope of the invention as claimed and, accordingly, the claims are definite.

Nonetheless, Applicants note that the Federal Circuit has stated that, in ordinary patent parlance, the "claim limitation 'a,' without more, requires *at least one*." *AbTox, Inc. v. Exitron Corp.*, 43 USPQ2d 1545, 1548 (Fed. Cir. 1997) (emphasis added). This term is ubiquitous in claim language without rendering such claims indefinite. In light of the identified authority, and solely for the purposes of expediting prosecution, Applicants have therefore amended the claims to replace the term "at least one" with the equivalent term "a." Applicants respectfully submit that the Examiner's concerns are alleviated and request that the rejection be withdrawn.

Claims 9, 10, 29, and 30 stand rejected for reciting "a sufficient concentration," "at least one tonicifying agent," and "such that." Specifically, the Examiner contends that the claim does not specify how many tonicifying agents and what concentrations are included in the composition, and whether the composition is isotonic." This rejection is respectfully traversed.

As indicated above, there is no rule that open-ended claims are indefinite. Furthermore, the Patent Act "requires only reasonable precision in delineating the bounds of the claimed invention." *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Where dimensions or concentrations are recited, "[a]s long as those of ordinary skill in the art realized that the dimensions could be easily obtained, Section 112, second paragraph, requires nothing more." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ 2d 1081 (Fed. Cir. 1986).

The specification provides:

> [I]n one embodiment, the pharmaceutical composition contains a sufficient concentration of at least on tonicifying agent such that the composition is isotonic.
>
> By "isotonic" is meant a solution in which a cell will neither shrink nor swell. An example of an isotonic solution is 0.9% sodium chloride in water. Typically, an isotonic solution will have about the same osmotic pressure as the fluid phase of a subject's cells or tissue. However, a solution that is isosmotic with intracellular fluid will not be isotonic if it contains a solute that freely permeates cell membranes. To determine is a solution is isotonic, it is necessary to identify the concentration of solutes at which cells will retain their normal size and shape. Methods of determining the isotonicity of a solution are known to

> those skilled in the art. See, for example, Setnikar *et al.* (1959) *JAPhA Sci Ed* 48:628.

Specification, page 16, lines 11-19. Further,

> [t]hose skilled in the art are familiar with a variety of pharmaceutically acceptable solutes useful in providing isotonicity in pharmaceutical compositions. Thus, the compositions of the invention further encompass components that can be used to provide isotonicity, for example, sodium chloride, glycine, mannitol, glycerol, sucrose, and other carbohydrates, acetic acid, other organic acids or their salts, and relatively minor amounts of citrates or phosphates. The ordinary skilled person would know of additional agents that are suitable for providing optimal tonicity.

Specification, page 16, line 25 continuing through page 17, line 4. As indicated, those of skill in the art would be apprised of what is meant by the claim terms, and would realize that tonicifying agents, and methods for providing optimal tonicity, could easily be obtained.

Further, although Applicants maintain that the phrase "at least one" does not render the claims indefinite, claims 9 and 29 have been amended in light of authority identified above, and solely for the purposes of expediting prosecution, to replace the phrase "at least one" with the equivalent "a." Support for these amendments can be found in original claims 9 and 29. Applicants respectfully submit that the Examiner's concern regarding this phrase is alleviated.

For all of these reasons, Applicants submit that the claims are definite, and respectfully request that the rejection be withdrawn.

Claims 11 and 12 are rejected as indefinite for reciting "a biologically active variant thereof." The Examiner indicates it is unclear what sequence the variant of human IGF-I has. This rejection is respectfully traversed.

In contrast to the Examiner's statement, the variant of human IGF-I has at least 70% sequence identity with the amino acid sequence for human IGF-I and has IGF-I activity. The specification teaches that:

> IGF-I variants differ from naturally occurring IGF-I molecules due to chemical modification or to amino acid insertions, deletions, substitutions (including chemically modified amino acids), and carboxy or amino terminal truncations or fusions. Such variants should substantially or completely retain IGF-I activities

> sufficient for the beneficial treatment of a given disorder. In particular, variants should retain the ability to bind to IGF-I receptor sites. IGF-I variants are known to those skilled in the art. See, for example, U.S. Patent No. 5,374,620.

Specification, page 9, lines 8-14. Further, methods for generating variants of IGF-I, such as human IGF-I recited in these claims, are well known in the art, and further described in the specification at page 10, lines 1-25, and page 11, line 26, continuing through page 12, line 25. In addition, one of skill in the art would understand the meaning of the phrase "at least 70% sequence identity," and the specification provides further guidance regarding determination of sequence identity. See the specification at pages 10, line 26, continuing through page 11, line 25. Examples of biologically active variants of human IGF-I are well known in the art and further described in the specification at page 9, line 14, and page 12, lines 10-25. Methods for determining IGF-I activity are also well known in the art, and further guidance is provided in the specification at page 13, lines 7-16.

To summarize, the phrase "a biologically active variant thereof" is an art-recognized term, and biologically active variants of human IGF-1 are known. Therefore, given the extensive disclosure of the specification, the phrase would be understood by one of skill in the art and would reasonably apprise one of skill in the art of the scope of the claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Rejections of the Claims Under 35 U.S.C. §102(b) Should Be Withdrawn

Claims 1-3, 6-10, and 13-14 stand rejected under 35 U.S.C. §102(b). In the Office Action, it is asserted that Bontempo *et al.* (hereinafter "EP '249") discloses a pharmaceutically active agent in a 50 mM succinate buffer "which is about 30 or 40 mM of succinate." (Office Action mailed April 17, 2002, at page 4, item 8). This rejection is respectfully traversed.

"It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). In construing the claims, the PTO is limited to the broadest reasonable interpretation. *In re Donaldson Company, Inc.*, 29 USPQ 2d 1845 (Fed. Cir. 1994) (*in banc*). This interpretation must be consistent with the specification. *In re Hyatt*, 54 USPQ 2d 1664 (Fed. Cir. 2000).

The specification teaches that suitable concentration ranges include an upper boundary of "less than about 50 mM, less than about 45 mM, less than about 40 mM, less than about 35 mM, less than about 30 mM." Page 7, lines 25-27. In light of this teaching, 50 mM is clearly *not* "about 30 or 40 mM." If 50 mM was "about 30 or 40 mM," Applicants would not have recited 50 mM separately from 45, 40, 35, and 30 mM. Therefore, to construe claims reciting a limitation of "about 40 mM" or "about 30 mM" as reading on a reference teaching only 50 mM is to treat the teaching of the specification as mere redundancy. Such a construction is not reasonable. Therefore, claims 1-3, 6-10, and 13-14 do not read on a composition of 50 mM succinate.

For this reason, claims 1-3, 6-10, and 13-14 are not anticipated by EP '249. The rejection should be withdrawn accordingly.

Claims 1-8 and 13-14 stand rejected under 35 U.S.C. §102(b). In the Office Action, it is asserted that Hwang-Felgner *et al.* (hereinafter "the '265 patent") discloses gamma-interferon in a 6.8 mM succinate buffer "which is about 10 mM of succinate" (Office Action mailed April 17, 2002, at page 5, item 9). This rejection is respectfully traversed.

The specification teaches that suitable concentration ranges include "about 0.5-140 mM; about 1-130 mM; about 2-120 mM; about 3-110 mM; about 4-100 mM; about 5-90 mM; about 6-80 mM; about 7-70 mM; about 8-60 mM; about 9-50 mM; about 10-40 mM; about 11-30 mM; about 12-25 mM; about 13-20 mM; about 14-19 mM; and about 15 mM." Page 7, lines 18-22. Based upon the specific teaching of separate ranges with separate lower boundaries, one of skill in the art would not reasonably conclude that a range having a lower boundary of "about 7 mM" is the same as a range having a lower boundary of "about 10 mM." Thus, reading claims 1-8 and 13-14 (which specify "about 10 mM") on a reference that discloses 6.8 mM succinate is not reasonable. Applicants respectfully submit that these claims are not anticipated by the '265 patent, and the rejection should be withdrawn.

Claims 1-8 and 13 stand rejected under 35 U.S.C. §102(b) over Sato *et al.* (hereinafter "the '555 patent"). In the Office Action, it is asserted that the '555 patent discloses interferon "at

a concentration of 0.01-0.2 mole/kg composition...which is about 10-200 mM of succinate" (Office Action mailed April 17, 2002, at page 5, item 10). This rejection is respectfully traversed.

As an initial matter, the '555 patent does not set forth the same range limitation as that claimed by Applicants and identified by Applicants as being a preferred range of succinate concentrations to provide for reduced pain upon injection of a pharmaceutical composition. Further, claim 1 has been amended to clarify the invention. As amended, claim 1 and dependent claims thereon are drawn to "[a] sterile injectable pharmaceutical composition." Support for this amendment can be found in the specification at page 19, lines 17-22.

By comparison, the '555 patent discloses "a pharmaceutical composition for treating keratosic disorders of skin and mucosa by *topical* administration." Column 2, lines 27-28 (emphasis added). The '555 patent specification teaches that the composition is in a "form suitable for topical or local application such as an ointment, a paste, a gel, a spray, a liquid and the like." Column 3, line 68, to column 4, line 2. It then teaches only external or topical application of the composition. Column 4 *et seq*. Further, the '555 patent does not teach that the composition is sterile.

Based on the foregoing reasons, the composition of the '555 patent does not meet all of the elements of the amended claims. Therefore, the rejection should not be applied to the claims as amended.

Claims 1-3 and 13 stand rejected under 35 U.S.C. §102(b). In the Office Action, it is asserted that Olefsky *et al.* (hereinafter "WO 96/40894") discloses protein kinase C antagonist in "a succinate buffer at concentration of 0.05 M which is about 30 or 40 mM of succinate" (Office Action mailed April 17, 2002, at page 5, item 11). This rejection is respectfully traversed.

As indicated above, the specification teaches that suitable concentration ranges include an upper boundary of "less than about 50 mM, less than about 45 mM, less than about 40 mM, less than about 35 mM, less than about 30 mM." Page 7, lines 25-27. For the reasons already stated, a construction in which "about 30 or 40 mM" is interpreted to read on 50 mM is not reasonable.

Accordingly, claims 1-3 and 13 do not read on, and are not anticipated by, WO 96/40894. The rejection should therefore be withdrawn.

CONCLUSION

In view of the aforementioned remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §112, second paragraph, and §102 are overcome. Applicants thank the Examiner for indicating that claims 21-28 and 31-34 are allowable. It is submitted that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on August 6, 2002.

Nora C. Martinez

Version with Markings to Show Changes Made:

In the Claims

Please amend the claims as follows:

1. (Twice amended) A sterile injectable pharmaceutical composition comprising [at least one] a pharmaceutically active agent and a buffer, wherein said buffer consists substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion.

9. (Amended) The composition of claim 1, further comprising a sufficient concentration of [at least one] a tonicifying agent such that the composition is isotonic.

29. (Amended) The composition of claim 21, further comprising a sufficient concentration of [at least one] a tonicifying agent such that the composition is isotonic.